4- 309 61 / P1

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Dated 23 March 2000

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# 1/77

## Request for grant of a patent

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| | | |
|---|---|---|
| 1. | Your reference | 4-30961/P1 |
| 2. | Patent application number *(The Patent Office will fill in this part)* | 21 MAY 1999 **9911926.5** |
| 3. | Full name, address and postcode of the or of each applicant *(underline all surnames)* | **DR. TETSUJI OKUNO**<br>**1259-1, KAMINARA, KUMAGAYA**<br>**SAITAMA PREFECTURE**<br>**360-0805, JAPAN** |
| | Patent ADP number *(if you know it)* | 7666555 001 |
| | If the applicant is a corporate body, give the country/state of its incorporation | |
| 4. | Title of invention | **Organic compounds** |
| 5. | Name of your agent *(If you have one)* | |
| | "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* | **B.A. YORKE & CO.**<br>**CHARTERED PATENT AGENTS**<br>**COOMB HOUSE, 7 ST. JOHN'S ROAD**<br>**ISLEWORTH**<br>**MIDDLESEX TW7 6NH** |
| | Patents ADP number *(if you know it)* | **1800001** |

| 6. If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number | Country | Priority application number *(if you know it)* | Date of filing (day/month/year) |
|---|---|---|---|
| | | | |

| 7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application | Number of earlier application | Date of filing (day/month/year) |
|---|---|---|
| | | |

| 8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*<br>*a) any applicant named in part 3 is not an inventor, or*<br>*b) there is an inventor who is not named as an applicant, or*<br>*c) any named applicant is a corporate body.*<br>*(see note (d))* | **Yes** |
|---|---|

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| Continuation sheets of this form | |
| Description | **17** |
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| Abstract | **1** |
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10. If you are also filing any of the following, state how many against each item.

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| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | **One** |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application

| Signature | Date |
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| B.A. Yorke & Co. | |
| **B.A. Yorke & Co.** | **21.05.99** |

12. Name and daytime telephone number of person to contact in the United Kingdom

**Mrs. E. Cheetham**
**0181 560 5847**

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# ORGANIC COMPOUNDS

This invention relates to organic compounds, in particular to bisphosphonates and to new therapeutic uses of bisphosphonates.

Bisphosphonates have recently become available for long-term treatment of patients with Multiple Myeloma (MM). These pyrophosphate analogs not only reduce the occurrence of skeletal related events but they also provide patients with clinical benefit and improve survival. Bisphosphonates are able to prevent bone resorption *in vivo*; the therapeutic efficacy of bisphosphonates has been demonstrated in the treatment of Paget's disease of bone, tumour-induced hypercalcemia and, more recently, bone metastasis and multiple myeloma (MM) (for review see Fleisch H 1997 Bisphosphonates clinical. In Bisphosphonates in Bone Disease. From the Laboratory to the Patient. Eds: The Parthenon Publishing Group, New York/London pp 68-163). The mechanisms by which bisphosphonates inhibit bone resorption are still poorly understood and seem to vary according to the bisphosphonates studied. Bisphosphonates have been shown to bind strongly to the hydroxyapatite crystals of bone, to reduce bone turn-over and resorption, to decrease the levels of hydroxyproline or alkaline phosphatase in the blood, and in addition to inhibit both the activation and the activity of osteoclasts.

MM is a plasma-cell malignancy characterized by the proliferation and the accumulation of malignant plasma cells within the bone marrow. The main clinical consequences are lytic bone lesions associated with pathologic fractures and bone pain. These lesions result from an excessive bone resorption, frequently leading to hypercalcemia. Bisphosphonates have been introduced for the long-term treatment of MM in combination with conventional chemotherapy. It has been shown recently that bisphosphonates such as clodronate and pamidronate can reduce the occurrence of skeletal related events such as lytic bone lesions and pathologic fractures and can relieve bone pain and improve the quality of life of patients.

I have now surprisingly found that certain bisphosphonates have an embolic effect on the newly formed capillary blood vessels which form during angiogenesis associated with tumour growth and invasion and certain other pathological conditions such inflammation, rheumatoid arthritis and osteoarthritis.

Accordingly the present invention provides a method for the embolic treatment of angiogenesis in a patient in need of such treatment which comprises administering an effective amount of a bisphosphonate to the patient.

The invention further provides use of a bisphosphonate in the preparation of a medicament for the embolic treatment of angiogenesis.

The invention yet further provides use of a bisphosphonate to treat or reverse angiogenesis associated with diseases or pathological conditions in mammals.

The invention also provides the use of a bisphosphonate as an angiogenesis reversing agent.

Angiogenesis, the formation of new blood vessels, is an essential event in many physiological processes such as wound repair, ovulation, and embryogenesis. Neovascularization is also a key component of many pathological events such as inflammation, myocardial ischemia, rheumatoid arthritis, osteoarthritis and tumour formation, e.g. tumour growth, invasion or metastasis. Many solid tumours induce the formation of new capillary blood vessels from the host vascular bed to supply nutrients and oxygen. Thus the invention is generally applicable to the treatment of diseases and medical conditions which involve angiogenesis during establishment or progression of the disease or condition, including those mentioned above. Further and more specific examples of diseases and conditions involving angiogenesis which may be treated using the invention include: retinopathies, e.g. diabetic retinopathy, psoriasis, haemangioblastoma, haemangioma, pain, age-related macular degeneration, and especially neoplastic diseases (solid tumours), such as especially breast cancer, cancer of the colon, lung cancer (especially small cell lung cancer, or cancer of the prostate.

The uses and methods of the present invention represent an improvement to existing therapy of malignant diseases in which bisphosphonates are used to prevent or inhibit development of bone metastases or excessive bone resorption, and in the therapy of inflammatory diseases such as rheumatoid arthritis and osteoarthritis. Use of bisphosphonates to embolise

n[illegible]y formed blood vessels has been found to lead to suppression of bone metastases and even reduction in size of bone metastases after appropriate periods of treatment. It has been observed using angiography that newly formed blood vessels disappear after bisphosphonate treatment, but that normal blood vessels remain intact. Further it has been observed that the embolised blood vessels are not restored following cessation of the bisphosphonate treatment. Also it has been observed that bone metastasis, rheumatoid arthritis and osteoarthritis patients experience decreased pain following bisphosphonate treatment.

In the present description the terms "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as ill patients.

Although the mode of action of bisphosphonates as agents which cause embolism of newly formed blood vessels is not known, it appears that the newly formed blood vessels (capillaries) become blocked, partially or completely obliterated or angiogenesis is otherwise reversed, leading to a partial or complete disappearance of the newly formed blood vessels (capillaries), for instance, when the tumour or disease site, e.g. site of inflammation, is viewed using angiography. For the purposes of the present description the terms "embolic treatment of angiogenesis" or "embolic effect" refer to these observed phenomena.

The bisphosphonates used in the present invention are typically those which can give rise to an embolic effect as described above.

Thus, for example, suitable bisphosphonates for use in the invention may include the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), e.g. pamidronate (APD); 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. dimethyl-APD; 4-amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), e.g. alendronate; 1-hydroxy-ethidene-bisphosphonic acid, e.g. etidronate; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, e.g. ibandronate; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid, e.g. amino-hexyl-BP; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g.

n yl-pentyl-APD (= BM 21.0955); 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), e.g. risedronate, including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 1-(4-chlorophenylthio)methane-1,1-diphosphonic acid (tiludronic acid), e.g. tiludronate; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, e.g. EB 1053 (Leo); 1-(N-phenyl-aminothiocarbonyl)methane-1,1-diphosphonic acid, e.g. FR 78844 (Fujisawa); 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, e.g. U-81581 (Upjohn); 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, e.g. YM 529; and 1,1-dichloromethane-1,1-diphosphonic acid (clodronic acid), e.g. clodronate.

Pharmaceutically acceptable salts are preferably salts with bases, conveniently metal salts derived from groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, including alkali metal salts, e.g. potassium and especially sodium salts, or alkaline earth metal salts, preferably calcium or magnesium salts, and also ammonium salts with ammonia or organic amines.

Especially preferred pharmaceutically acceptable salts are those where one, two, three or four, in particular one or two, of the acidic hydrogens of the bisphosphonic acid are replaced by a pharmaceutically acceptable cation, in particular sodium, potassium or ammonium, in first instance sodium.

A very preferred group of pharmaceutically acceptable salts is characterized by having one acidic hydrogen and one pharmaceutically acceptable cation, especially sodium, in each of the phosphonic acid groups.

All the bisphosphonic acid derivatives mentioned above are well known from the literature. This includes their manufacture (see e.g. EP-A-513760, pp. 13-48). For example, 3-amino-1-hydroxypropane-1,1-diphosphonic acid is prepared as described e.g. in US patent 3,962,432 as well as in US patents 4,639,338 and 4,711,880, and 1-hydroxy-2-(imidazol-1-yl)-ethane-1,1-diphosphonic acid is prepared as described e.g. in US patent 4,939,130.

A particular embodiment of the invention is represented by the use of a bisphosphonic acid derivative which is selected from 3-amino-1-hydroxypropane-1,1-diphosphonic acid, 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid; 4-amino-1-hydroxybutane-1,1-diphosphonic acid; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid, 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid, and N-methyl pyridinium salts thereof; 1-(4-chlorophenylthio)methane-1,1-diphosphonic acid; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid; 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid; 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester; 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid; or a pharmaceutically acceptable salt thereof, and any hydrate thereof.

A preferred embodiment of the invention is represented by the use of a bisphosphonic acid derivative which is selected from 3-amino-1-hydroxypropane-1,1-diphosphonic acid; 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid; 4-amino-1-hydroxybutane-1,1-diphosphonic acid; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)-propane-1,1-diphosphonic acid; 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid; or a pharmaceutically acceptable salt thereof, and any hydrate thereof.

A very preferred embodiment of the invention is represented by the use of a methane-bisphosphonic acid derivative which is selected from pamidronic acid, alendronic acid, 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-2-(imidazol-1--yl)ethane-1,1-diphosphonic acid; risedronic acid and tiludronic acid; or a pharmaceutically acceptable salt thereof, and any hydrate thereof.

An especially preferred embodiment of the invention is represented by the use of a bisphosphonic acid derivative which is selected from 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-

d' osphonic acid and 3-amino-1-hydroxypropane-1,1-diphosphonic acid, or a pharmaceutically acceptable salt thereof, and any hydrate thereof.

Further the invention relates to the use of 3-amino-1-hydroxypropane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof or any hydrate thereof, e.g. pamidronate disodium or pamidronate.

Further the invention relates to the use of 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof or any hydrate thereof, e.g. zoledronate.

The bisphosphonates (hereinafter referred to as the Agents of the Invention) may be used in the form of isomer or of a mixture of isomers where appropriate, typically as optical isomers such as enantiomers or diastereoisomers or geometric isomers, typically cis-trans isomers. The optical isomers are obtained in the form of the pure antipodes and/or as racemates.

The Agents of the Invention can also be used in the form of their hydrates or include other solvents used for their crystallisation.

The Agents of the Invention (the bisphosphonates) are preferably used in the form of pharmaceutical compositions that contain a therapeutically effective amount of active ingredient optionally together with or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers which are suitable for administration.

The pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration, compositions for parenteral, such as intravenous or subcutaneous administration, or compositions for transdermal administration (e.g. passive or iontophoretic).

Preferably, the pharmaceutical compositions are adapted to oral or parenteral (especially intravenous, intra-arterial or transdermal) administration. Intra-arterial and oral, first and foremost intra-arterial, administration is considered to be of particular importance.

Preferably the bisphosphonate active ingredient is in the form of a parenteral, most preferably an intra-arterial form.

The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, hormonal status (e.g. post-menopausal) and bone mineral density as appropriate. Most preferably, however, the bisphosphonate is administered intra-arterially into an artery which leads to the site of the newly formed blood vessels.

Thus in particularly preferred embodiments the invention provides:

a method for the embolic treatment of angiogenesis in a patient in need of such treatment which comprises intra-arterially administering an effective amount of a bisphosphonate to the patient;

use of a bisphosphonate in the preparation of a medicament for the intra-arterial embolic treatment of angiogenesis;

intra-arterial use of a bisphosphonate to treat or reverse angiogenesis associated with diseases or pathological conditions in mammals; and

the intra-arterial use of a bisphosphonate as an angiogenesis reversing agent.

The dosage of the Agents of the Invention may depend on various factors, such as effectiveness and duration of action of the active ingredient, mode of administration, warm-blooded species, and/or sex, age, weight and individual condition of the warm-blooded animal.

Normally the dosage is such that a single dose of the bisphosphonate active ingredient from 0.002 - 3.40 mg/kg, especially 0.01 - 2.40 mg/kg, is administered to a warm-blooded animal weighing approximately 75kg. If desired, this dose may also be taken in several, optionally equal, partial doses.

"mg/kg" means mg drug per kg body weight of the mammal - including man - to be treated.

The dose mentioned above - either administered as a single dose (which is preferred) or in several partial doses - may be repeated, for example once daily, once weekly, once every month, once every three months, once every six months or once a year. In other words, the pharmaceutical compositions may be administered in regimens ranging from continuous daily therapy to intermittent cyclical therapy.

Preferably, the bisphosnates are administered in doses which are in the same order of magnitude as those used in the treatment of the diseases classically treated with methanebisphosphonic acid derivatives, such as Paget's disease, tumour-induced hypercalcaemia or osteoporosis. In other words, preferably the methanebisphosphonic acid derivatives are administered in doses which would likewise be therapeutically effective in the treatment of Paget's disease, tumour-induced hypercalcaemia or osteoporosis, i.e. preferably they are administered in doses which would likewise effectively inhibit bone resorption.

Formulations in single dose unit form contain preferably from about 1% to about 90%, and formulations not in single dose unit form contain preferably from about 0.1% to about 20%, of the active ingredient. Single dose unit forms such as capsules, tablets or dragées contain e.g. from about 1mg to about 500mg of the active ingredient.

Pharmaceutical preparations for enteral and parenteral administration are, for example, those in dosage unit forms, such as dragées, tablets or capsules and also ampoules. They are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, where appropriate granulating a resulting mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, into tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone and, if desired, disintegrators, such as the above-mentioned starches, also

carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating agents and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that may be resistant to gastric juices, there being used, inter alia, concentrated sugar solutions that optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or lacquer solutions in suitable organic solvents or solvent mixtures or, to produce coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colouring substances or pigments may be added to the tablets or dragee coatings, for example for the purpose of identification or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical preparations are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilisers to be added.

Parenteral formulations are especially injectable fluids that are effective in various manners, such as intravenously, intramuscularly, intraperitoneally, intranasally, intradermally, subcutaneously or preferably intra-arterially. Such fluids are preferably isotonic aqueous solutions or suspensions which can be prepared before use, for example from lyophilised preparations which contain the active ingredient alone or together with a pharmaceutically acceptable carrier. The pharmaceutical preparations may be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

Suitable formulations for transdermal application include an effective amount of the active ingredient with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal

d( :es are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the active ingredient of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The following Examples illustrate the invention described hereinbefore. The term "active ingredient" is to be understood as being any one of the bisphosphonic acid derivatives mentioned above as being useful according to the present invention.

## EXAMPLES

Example 1: Capsules containing coated pellets of active ingredient, for example, disodium pamidronate pentahydrate, as active ingredient:

Core pellet:

| | |
|---|---|
| active ingredient (ground) | 197.3 mg |
| Microcrystalline cellulose (Avicel® PH 105) | 52.7 mg |
| | 250.0 mg |

+ Inner coating:

| | |
|---|---|
| Cellulose HP-M 603 | 10.0 mg |
| Polyethylene glycol | 2.0 mg |
| Talc | 8.0 mg |
| | 270.0 mg |

+ Gastric juice-resistant outer coating:

| | |
|---|---|
| Eudragit® L 30 D (solid) | 90.0 mg |
| Triethyl citrate | 21.0 mg |
| Antifoam® AF | 2.0 mg |
| Water | |
| Talc | 7.0 mg |
| | 390.0 mg |

A mixture of disodium pamidronate with Avicel® PH 105 is moistened with water and kneaded, extruded and formed into spheres. The dried pellets are then successively coated in the fluidized bed with an inner coating, consisting of cellulose HP-M 603, polyethylene glycol (PEG) 8000 and talc, and the aqueous gastric juice-resistant coat, consisting of Eudragit® L 30 D, triethyl citrate

and Antifoam® AF. The coated pellets are powdered with talc and filled into capsules (capsule size 0) by means of a commercial capsule filling machine, for example Höfliger and Karg.

Example 2: Monolith adhesive transdermal system, containing as active ingredient, for example, 1-hydroxy-2-(imidazol-1-yl)-ethane-1,1-diphosphonic acid:

Composition:

| | |
|---|---|
| polyisobutylene (PIB) 300 (Oppanol B1, BASF) | 5.0 g |
| PIB 35000 (Oppanol B10, BASF) | 3.0 g |
| PIB 1200000 (Oppanol B100, BASF) | 9.0 g |
| hydrogenated hydrocarbon resin (Escorez 5320, Exxon) | 43.0 g |
| 1-dodecylazacycloheptan-2-one (Azone, Nelson Res., Irvine/CA) | 20.0 g |
| active ingredient | 20.0 g |
| Total | 100.0 g |

Preparation:

The above components are together dissolved in 150 g of special boiling point petroleum fraction 100-125 by rolling on a roller gear bed. The solution is applied to a polyester film (Hostaphan, Kalle) by means of a spreading device using a 300mm doctor blade, giving a coating of about 75 $g/m^2$. After drying (15 minutes at 60°C), a silicone-treated polyester film (thickness 75 mm, Laufenberg) is applied as the peel-off film. The finished systems are punched out in sizes in the wanted form of from 5 to $30cm^2$ using a punching tool. The complete systems are sealed individually in sachets of aluminised paper.

Example 3: Vial containing 1.0 mg dry, lyophilized 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid (mixed sodium salts thereof). After dilution with 1 ml of water, a solution (concentration 1 mg/ml) for i.v. infusion is obtained.

Composition:

| | | |
|---|---|---|
| active ingredient (free diphosphonic acid) | | 1.0 mg |
| mannitol | | 46.0 mg |
| Trisodium citrate x 2 $H_2O$ | ca. | 3.0 mg |
| water | | 1 ml |
| water for injection | | 1 ml . |

In 1 ml of water, the active ingredient is titrated with trisodium citrate x 2 $H_2O$ to pH 6.0. Then, the mannitol is added and the solution is lyophilized and the lyophilisate filled into a vial.

Example 4: Ampoule containing active ingredient, for instance disodium pamidronate pentahydrate dissolved in water. The solution (concentration 3 mg/ml) is for i.v. infusion after dilution.

Composition:

| | |
|---|---|
| active ingredient | 19.73 mg |
| ( ≙ 5.0 mg of anhydrous active ingredient) | |
| mannitol | 250 mg |
| water for injection | 5 ml . |

Example 5 Treatment of Patients

A number of patients suffering with cancers and associated metastases and one patient suffering with osteoarthritis are treated with bisphosphonate infusions intra-arterially through arteries leading to the cancer, metastasis or osteoarthritic sites. The cancer, metastasis and osteoarthritic sites are examined using standard angiographic techniques both prior to and after bisphosphonate infusion. In all cases a marked embolic effect on the newly formed capillary and other blood vessels in the region the disease site is observed. The treatment regimes are described in greater detail below.

i) Patient ID: 1676
Gender: Female
Age: 68y 6m
Diagnosis: Breast Cancer, multiple lung metastases
Therapeutic pedicles: the bilateral bronchial arteries

A total of 75 mg of pamidronate disodium (Aredia®) to obliterate their tumour blushes.

ii) Patient ID: 2022
Gender: Female
Age: 57y 1m
Diagnosis: Breast Cancer, bone metastasis, multiple lung metastases
Therapeutic pedicles 1. bilateral intercostal arteries to 12th intercostal artery
2. bilateral bronchial arteries
3. lateral internal thoracic artery
4. vr. lateral thoracic artery

A total of 75 mg of pamidronate disodium (Aredia®), 100 mg of etoposide, 10 mg of BLM and 500mg of impr as-liprodol. is utilized to obliterate the tumour blushes which are located along these pedicles. (for bone metastases pamidronte is solely used)

iii) Patient ID: 1441

Gender: Female

Age: 63y 11m

Diagnosis: Breast Cancer, multiple bone metastases, multiple hepatic metastases

Therapeutic pedicles: 1. bilateral arteries

2. bilateral L 4/5 to L1 lumbar arteries

3. right hepatic s 6,7,8 subergemenal hepatic arteries

A total of 45 mg of pamidronate disodium (Aredia®), 10 mg of ADM (for hepatic) and 500mg of impr as-liprodol emulsion are utilized to obliterate the tumour blushes, which are located along these pedicles (for bone metastases, 45 mg of pamidronate is used on its own and for hepatic metastases 10 mg of ADM (for hepatic) with 500mg of impr as-liprodol is additionally utilized).

iv) Patient ID: 1840

Gender: ???

Age: 43y 11m

Diagnosis: Tongue Cancer, colateral vibo, diaphragm metastasis

Therapeutic pedicles: 1. the 7,8,9,10th intercostal arteries

2. lt. ing. phrenia

3. lt. higher intercostal artery

4. lt. subscapular artery

A total of 60 mg of pamidronate disodium (Aredia®) is infused into the tumour to obliterate their tumour blushes, which are located along these pedicles.

v) Patient ID: 1835

Gender: Female

Age: 34y 8m

| | |
|---|---|
| Diagnosis: | Breast cancer, multiple lung metastases, multiple bone metastases, multiple hepatic metastases |
| Therapeutic pedicles | lt. ileo lumbar, ileo saisal, lateral saisal arteries<br>rt. ileo lumbar, deep ilcal orumgles arteries<br>bilat. L4, lt L3, bilat L2 l thor. arteries, rt. thor. intercostal arteries, bronchial, rt. hepatic artery. |

A total of 90 mg of pamidronate disodium (Aredia®), 100 mg of etoposide, 10 mg of ADM, 6.0 CE of OK-432, and 500mg of impr as-liprodol emulsion is utilized to obliterate the tumour blushes, which are located along these pedicles.

vi)

| | |
|---|---|
| Patient ID: | 2013 |
| Gender: | |
| Age: | 73y 7m |
| Diagnosis: | Right knee joint osteoarthritis<br>(interpreted as an ischemic angiogenic bone disorder) |
| Therapeutic pedicles: | 1. right descending gericular artery<br>2. right sular artery |

A total of 30 mg of pamidronate disodium (Aredia®) is utilized to obliterate the tumour blushes which are located along these pedicles.

vii)

| | |
|---|---|
| Patient ID: | 2026 |
| Gender: | Female |
| Age: | 49y |
| Diagnosis: | Breast Cancer, Thoracic spine, bone metastases |
| Therapeutic pedicles: | 1. bilateral highest intercostal arteries<br>2. bilateral 1-4 lumbar arteries<br>3. median sasd artery |

A total of 30 mg of pamidronate disodium (Aredia®) is infused into the tumour blushes to obliterate them.

viii) Patient ID: 1985
Gender: Female
Age: 49y 8m
Diagnosis: Breast Cancer, multiple bone metastases
After BCT
Therapeutic pedicles arteries
1. The bilateral highest intercostal to 12th intercostal
2.The bilateral lumbar arteries (L1 to L4)
3. the median pausal artery

A total of 90 mg of pamidronate disodium (Aredia®), is utilized to obliterate the tumour blushes, which are located along these pedicles.

ix) Patient ID: 1063
Gender:
Age: 80y 10m
Diagnosis: Lung Cancer, squamous cell cancer
Therapeutic pedicles: 1. right highest intercostal artery
2. common trunk of the bilateral bronchial arteries

A total of 45 mg of pamidronate disodium (Aredia®), is solely infused into the tumour to obliterate the tumour blushes of the feeder pedicles.

## CLAIMS

1. A method for the embolic treatment of angiogenesis in a patient in need of such treatment which comprises administering an effective amount of a bisphosphonate to the patient.

2. Use of a bisphosphonate in the preparation of a medicament for the embolic treatment of angiogenesis.

3. Use of a bisphosphonate to treat or reverse angiogenesis associated with diseases or pathological conditions in mammals.

4. Use of a bisphosphonate as an angiogenesis reversing agent.

5. A method according to claim 1 or a use according to claim 2, 3 or 4 for the treatment of inflammation, myocardial ischemia, rheumatoid arthritis, osteoarthritis and tumour formation, e.g. tumour growth, invasion or metastasis.

6. A method according to claim 1 or a use according to claim 2, 3 or 4, in which the bisphosphonate is selected from the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), e.g. pamidronate (APD); 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. dimethyl-APD; 4-amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), e.g. alendronate; 1-hydroxy-ethidene-bisphosphonic acid, e.g. etidronate; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, e.g. ibandronate; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid, e.g. amino-hexyl-BP; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. methyl-pentyl-APD (= BM 21.0955); 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), e.g. risedronate, including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 1-(4-chlorophenylthio)methane-1,1-diphosphonic acid (tiludronic acid), e.g. tiludronate; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-

hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, e.g. EB 1053 (Leo); 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid, e.g. FR 78844 (Fujisawa); 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, e.g. U-81581 (Upjohn); 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, e.g. YM 529; and 1,1-dichloromethane-1,1-diphosphonic acid (clodronic acid), e.g. clodronate..

7. A method according to claim 1 or a use according to claim 2, 3 or 4, in which the bisphosphonate is pamidronate or zoledronate, or a pharmaceutically acceptable salt thereof, or any hydrate thereof.

8. A method for the embolic treatment of angiogenesis in a patient in need of such treatment which comprises intra-arterially administering an effective amount of a bisphosphonate to the patient;
use of a bisphosphonate in the preparation of a medicament for the intra-arterial embolic treatment of angiogenesis;
intra-arterial use of a bisphosphonate to treat or reverse angiogenesis associated with diseases or pathological conditions in mammals; and
the intra-arterial use of a bisphosphonate as an angiogenesis reversing agent.

9. A method or use according to claim 8, in which the bisphosphonate is pamidronate or zoledronate, or a pharmaceutically acceptable salt thereof, or any hydrate thereof.

10. All novel compositions uses and methods substantially as hereinbefore described with particular reference to the description and Examples.

## ABSTRACT

## ORGANIC COMPOUNDS

A method for the embolic treatment of angiogenesis in a patient in need of such treatment, e.g. a tumour patient or a patient suffering from an inflammatory disease, which comprises administering , preferably via an intra-arterial route, an effective amount of a bisphosphonate, e.g. pamidronate or zoledronate or salts or hydrates thereof, to the patient